

000005

Proposed Generic Labeling

PROPOSED GENERIC PRODUCT LABELING

NADA No. XXX-XXX, Approved by FDA (NOTE: NADA # to be determined)
Intervet Inc.

XXX mL Multiple-Dose Vial [NOTE: Vial size(s) to be determined]

"TRADENAME" INJECTABLE SOLUTION 450 mg/ml
 (Florfenicol)

For intramuscular and subcutaneous use in cattle only.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: "TRADENAME" Injectable is a solution of the synthetic antibiotic florfenicol. Each millimeter of sterile "TRADENAME" Injectable Solution contains 450 mg of florfenicol (NOTE: Excipients to be determined).

CLINICAL PHARMACOLOGY: The pharmacokinetic disposition of florfenicol injectable solution was evaluated in feeder calves following single intramuscular administration at the recommended dose of 20 mg/kg. Florfenicol injectable solution was also administered intravenously to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability¹ (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C _{MAX} (µg/mL)	3.07*	1.43 - 5.60
T _{MAX} (hr)	3.33	0.75 - 8.00
T _{1/2} , (hr)	18.3**	8.30 - 44.0
AUC (µg•min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd _{ss} (L/kg)***	0.77	0.68 - 0.85
Cl _t (mL/min/kg)***	3.75	3.17 - 4.31

* harmonic mean

** mean value

*** following I.V. administration

C_{MAX} Maximum serum concentration

T_{MAX} Time at which C_{MAX} is observed

T_{1/2} Biological half-life

AUC Area under the curve

Vd_{ss} Volume of distribution at steady state

Cl_t Total body clearance

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively.

MICROBIOLOGY: Florfenicol is a synthetic, broad-spectrum antibiotic active against many gram-negative and gram-positive bacteria isolated from domestic animals. It is primarily bacteriostatic and acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. *In vitro* and *in vivo* activity has been demonstrated against commonly isolated bacterial pathogens involved in bovine respiratory disease (BRD), including *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*, as well as against commonly isolated bacterial pathogens involved in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

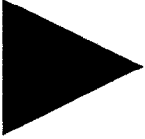
TABLE 2. MIC Values* of Florfenicol Against Bacterial Isolates From Natural Infection of Cattle

Organism	Isolate Numbers	MIC ₅₀ ** (µg/mL)	MIC ₉₀ ** (µg/mL)
<i>Pasteurella haemolytica</i>	398	0.50	1.00
<i>Pasteurella multocida</i>	350	0.50	0.50
<i>Haemophilus somnus</i>	66	0.25	0.50
<i>Fusobacterium necrophorum</i>	33	0.25	0.25
<i>Bacteroides melaninogenicus</i>	20	0.25	0.25


* The correlation between the *in vitro* susceptibility data (MIC values) and clinical response has not been determined.

**The minimum inhibitory concentration for 50% and 90% of the isolates.

INDICATIONS: "TRADENAME" Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*, and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*.



RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.



WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call XXX-XXX-XXXX. (NOTE: Phone number to be determined.)

CAUTION: Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

ADVERSE EFFECTS: Inappetance, decreased water consumption, or diarrhea may occur transiently following treatment.

TOXICOLOGY: A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased bodyweight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group.

Decreased feed and water consumption, bodyweight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.

A 43-day controlled study was conducted in healthy cattle to evaluate effects of florfenicol injectable solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, florfenicol injectable solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

DOSAGE AND ADMINISTRATION: For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): "TRADENAME" Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (2 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, "TRADENAME" Injectable Solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (4 mL/100 lbs). Do not administer more than 10 mL at each site. **The injection should be given only in the neck.**

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high-risk of developing BRD: "TRADENAME" Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (4 mL/100 lbs). Do not administer more than 10 mL at each site. **The injection should be given only in the neck.**

"TRADENAME" Dosage Guide		
ANIMAL WEIGHT (lbs)	IM "TRADENAME" Dosage 2.0 mL/100 lb Body Weight (mL)	SC "TRADENAME" Dosage 4.0 mL/100 lb Body Weight (mL)
100	2.0	4.0
200	4.0	8.0
300	6.0	12.0
400	8.0	16.0
500	10.0	20.0
600	12.0	24.0
700	14.0	28.0
800	16.0	32.0
900	18.0	36.0
1000	20.0	40.0

Recommended Injection Location (NOTE: Picture of cow and syringe showing recommended injection location will be inserted as pictured on pioneer label.)

Do not inject more than 10 mL per injection site.

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

STORAGE CONDITIONS: Store between 2°-30°C (36°-86°F). Refrigeration is not required. The solution is XXXXX to XXXXX colored (Note: Color to be determined). Color does not affect potency.

HOW SUPPLIED: "TRADENAME" Injectable Solution is packaged in XXX mL glass sterile multiple-dose vials. [Note: Vial size(s) to be determined.]

REFERENCE: 1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. *J Vet Pharmacol Therap.* 1994; 17:253-258.



Distributed by:
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